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# Acetylcholine modulation of short-term plasticity is critical to reliable long-term plasticity in hippocampal synapses

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CA3-CA1 synapses in the hippocampus are the initial locus of episodic memory. The action of acetylcholine alters cellular excitability, modifies neuronal networks, and triggers secondarysignaling that directly affects long-term plasticity (LTP) (the cellular underpinning of memory). It is therefore considered a critical regulator of learning and memory in the brain. Its action via M4 metabotropic receptors in the presynaptic terminal of the CA3 neurons and M1 metabotropic receptors in the postsynaptic spines of CA1 neurons produce rich dynamics across multiple timescales. We developed a model to describe the activation of postsynaptic M1 receptors that leads to IP3 production from membrane PIP2 molecules. The binding of IP3 to IP3 receptors in the endoplasmic reticulum (ER) ultimately causes calcium release. This calcium release from the ER activates potassium channels like the calcium-activated SK channels and alters different aspects of synaptic signaling. In an independent signaling cascade, M1 receptors also directly suppress SK channels and the voltage-activated KCNQ2/3 channels, enhancing post-synaptic excitability. In the CA3 presynaptic terminal, we model the reduction of the voltage sensitivity of voltage-gated calcium channels (VGCCs) and the resulting suppression of neurotransmitter release by the action of the M4 receptors. Our results show that the reduced initial release probability because of acetylcholine alters short-term plasticity (STP) dynamics. We characterize the dichotomy of suppressing neurotransmitter release from CA3 neurons and the enhanced excitability of the postsynaptic CA1 spine. Mechanisms underlying STP operate over a few seconds, while those responsible for LTP last for hours, and both forms of plasticity have been linked with very distinct functions in the brain. We show that the concurrent suppression of neurotransmitter release and increased sensitivity conserves neurotransmitter vesicles and enhances the reliability in plasticity. Our work establishes a relationship between STP and LTP coordinated by neuromodulation with acetylcholine.

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